frequently metastasized to other organs. Furthermore, patients with bone marrow micrometastases were more likely to die of the disease, even among patients that received adjuvant therapy. In patients with very small tumours (less than 2 cm in diameter) without lymph node metastases, and who therefore did not receive adjuvant therapy, the presence of bone marrow micrometastases was also associated with shorter survival times.

The authors suggest that assays for the presence of bone marrow micrometastases could be a complementary approach to lymph node biopsies in determining which patients should receive adjuvant therapy.

Kristine Novak

References and links

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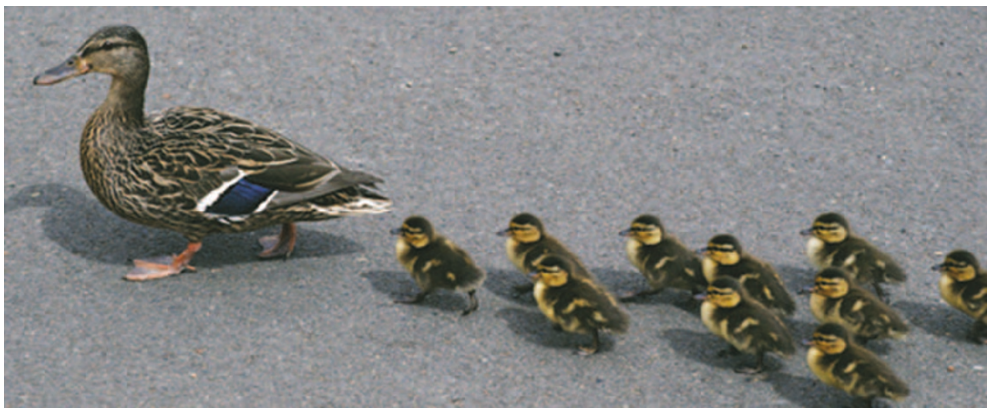
FURTHER READING Pantel, K. & Brakenhoff, R. H. Dissecting the metastatic cascade. *Nature Rev. Cancer* **4**, 448–456 (2004)

TUMOUR SUPPRESSORS

New additions



The genes that encode the p53 family members p63 and p73 enable the production of several different protein isoforms. In light of this fact, Jean-Christophe Bourdon, David Lane and colleagues have re-investigated the gene structure of the founding member, *TP53*. They found that *TP53* in fact encodes at least six different p53 mRNA isoforms, some of which are differentially regulated in cancer cells.

Mammalian genomes contain three members of the *TP53* family, yet only one form exists in invertebrates, implying that the mammalian members are derived from the triplication of one ancestral gene. If this hypothesis is correct, it is somewhat strange that *TP53* does not share the complexity of *TP63* and *TP73*, both of which can be transcribed from an alternative internal promoter and express at least 3 and 11 alternatively spliced isoforms, respectively. *TP53*, on the other hand, was thought to have a much simpler structure with only one promoter that transcribes three mRNA splice variants.

To assess *TP53* and all of its encoded mRNAs, Bourdon *et al.* used GeneRacer PCR, a technique that amplifies only capped mRNA transcripts and so allows the detection of the transcription initiation site. They also designed specific primers for exons four and five in an attempt to identify any transcripts that might be generated from an internal promoter.

The authors found that, altogether, *TP53* can theoretically transcribe nine different p53 isoforms. These are full length p53, p53β and p53γ, Δ133p53, Δ133p53β and Δ133p53γ (Δ133 owing to alternative internal promoters in intron four), and Δ40p53, Δ40p53β and Δ40p53γ (Δ40 owing to the alternative splicing of intron two or use of an alternative translation-initiation site). The β and γ isoforms arise from alternative splicing of intron nine. All of these mRNAs can be detected in normal human tissue samples in a tissue-specific manner and all of these mRNAs lead to protein expression. Endogenous p53β isoforms were detected by specific antibodies. However, isoform-specific antibodies still need to be generated to detect endogenous p53γ and Δ133p53 protein isoforms.

Do any of these isoforms affect p53 function? Further investigations showed that the p53β isoform binds the *BAX* promoter more readily than the *MDM2* promoter (or the *CDKN1A* promoter), whereas p53 preferentially binds *MDM2* over *BAX*. The authors show that this causes p53β to enhance p53-mediated *BAX* promoter activity, but that this does not seem to affect the level of apoptosis induced in cells expressing both p53 and p53β. On the other hand, Δ133p53 inhibits p53-mediated apoptosis, indicating that it can function as a dominant negative.

The authors also assessed expression of the mRNA isoforms in human breast tumour samples. None of the 30 samples expressed the same combination of p53 isoforms that is seen in normal breast tissue. For example, *TP53γ* and *TP53β*, which are expressed in normal breast tissue, were either not detected or detected in only ten samples, respectively. *Δ133TP53*, which is not expressed in normal breast tissue, was detected in 24 samples. Notably, only five of the tumours expressed a mutant form of p53.

On the basis of these findings, the authors conclude that the regulation of expression of the p53 isoforms seems to be altered in breast cancer, a finding that could be relevant in tumours that express wild-type p53.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Bourdon, J. C. *et al.* p53 isoforms can regulate p53 transcriptional activity. *Genes Dev.* 30 August 2005 (doi: 10.1101/gad.1339905)

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